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Defense and Counter-Defense in the *Drosophila* RNAi-based Immune System

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Introduction: Vertebrates depend on a sophisticated network of innate and adaptive immune responses for antiviral defense. Insects and other non-vertebrates, however, lack these responses; yet, they are able to effectively clear viral infections. We recently showed that RNA interference (RNAi) — post-transcriptional gene silencing guided by small interfering RNA (siRNA) — provides antiviral immunity in the fruitfly, *Drosophila melanogaster*. In antiviral RNAi, viral dsRNA is processed by the nuclease Dicer-2 into viral-siRNAs, which guide recognition of viral target RNAs by the effector complex RISC.

Viral suppressors of RNAi (VSR) allow viruses to replicate in the face of the potent RNAi-based antiviral immune system. We previously established that *Drosophila* C virus (DCV) 1A protein inhibits processing of long dsRNA by Dicer-2. Similarly, the Flock House Virus B2 protein inhibits RNAi via its dsRNA binding activity.

Methods: Using *Drosophila* as a model organism, we analyze the role of RNAi in antiviral defense in insects.

Results: The recently discovered Nora virus (NoraV) is a (+) RNA virus that establishes a persistent infection in flies. Small RNA sequencing identified viral siRNAs that mapped across the Noraviral genome, indicating that NoraV is targeted by an antiviral RNAi response. NoraV encodes four open reading frames (ORFs). Based on in vitro assays in the *Drosophila* S2 cell line, we identified Nora virus ORF1 as a viral RNAi suppressor. NoraV ORF1 suppresses RNAi that is induced by either long dsRNA or by 21-nt siRNAs. These results suggest that, unlike other characterized insect VSRs, NoraV ORF1 suppresses the effector phase of the RNAi pathway.

Discussion: Collectively, our data indicate that defense and viral counter-defense is a recurrent theme in the *Drosophila* RNAi-based immune system. The evolution of VSR activity may contribute to viral persistence.

Keywords: RNAi, Antiviral Defense, *Drosophila*, Innate immunity